REMARKS/ARGUMENTS

Status of the Claims

Claims 1, 2, 4, and 6-7 are currently pending. Claims 1, 4, and 7 have been amended to more particularly recite and distinctly claim the invention and claims 3 and 5 have been canceled. No new matter has been added by way of the amendments.

Rejections under Section 103

Claims 1-7 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Raffa (EP 0546676) and Mauskop (U.S. 5,914,129) in view of Saslawski (U.S. 6,372,255) and the Physicians' Desk Reference. Applicants traverse.

Although Raffa discloses the combination of a number of NSAIDs and tramadol, Raffa does not teach or suggest the specific combination of 0.0010-0.10000 g ketorolac and 0.0010-0.20000 g tramadol with the specific excipients: colloidal silicate dioxide, sodium glycolate starch, lactose, microcrystalline cellulose, and magnesium stearate, as recited in the instant claims. Further, there is no teaching that the recited combination of tramadol and ketorolac would produce a synergistic effect as applicants have discovered. Indeed, the low dose of tramadol and ketorolac present in the inventive compositions highlight the unexpected synergy exhibited by the recited combination. As evidence of the unpredictability of the effect of combining tramadol with NSAIDS, submitted herewith is a pending publication entitled "Co-administration of rofecoxib and tramadol results in additive or subadditive interaction during arthritic nociception in rat," *Pharmacology, Biochemistry, and Behavior*, accepted May 7, 2007, which teaches that combining tramadol with rofecoxib (a NSAID) produces an additive or sub-additive therapeutic effect, i.e., a no better than the combined therapeutic effect of each individual ingredient. As such, the pending publication provides evidence that combining tramadol with non-steroidal anti-inflammatory drugs (NSAIDS) does not necessarily yield predictable results, and clearly contradicts any expectation of synergy. In conclusion, Raffa's disclosure of tramadol and a long list of NSAIDs simply fails to teach or suggest the specific combination and ratios recited in the instant claims, and does not otherwise render obvious the claimed composition.

While Mauskop discloses NSAID compositions for the treatment of migraines, Mauskop does not teach or suggest combining tramadol with ketorolac at all, much less a composition comprising 0.0010-0.10000 g ketorolac and 0.0010-0.20000 g tramadol with the

specific excipients: colloidal silicate dioxide, sodium glycolate starch, lactose, microcrystalline cellulose, and magnesium stearate, as recited in the instant claims. As such, Mauskop, alone or in combination with any of the other cited references, also does not render obvious any of the instant claims.

Saslawski recites tablets comprising preferably 2 layers, or multilayers, (see column 2, lines 12-13), each layer may contain a different active ingredient, (column 2, lines 52-53). One feature of the first layer is that it disintegrates rapidly at the site of administration, whereas in contrast, the second layer is not biodegradable (column 2, lines 25-27). The instant invention refers to pharmaceutical compositions for alleviating pain in subjects in need thereof, by the administration of said composition in the form of a capsule, see original claim 5 (new claim 4). Capsules are designed to dissolve in the stomach and to start releasing their contents within minutes after swallowing, unlike the tablet of Saslawski that releases in an instant and prolonged fashion the two active agents used in its formulation. The synergistic effects of the resulting composition of the instant invention are measured in a period of from 15 to 45 minutes (see pages 4 and 5 of the instant invention's specification), whereas the releases of the first and second active agents are different, and therefore one cannot measure the synergy of the two substances as in the current invention has been done. In the light of this difference, it is not possible to compare the invention of Saslawski with the invention of the instant application.

Saslawski was cited as exemplary of excipients typically included in oral compositions, and the PDR was cited as disclosing salt forms of tramadol and ketorolac. However, neither of these references teaches or suggests combining ketorolac and tramadol in the recited ratios with colloidal silicate dioxide, sodium glycolate starch, lactose, microcrystalline cellulose, and magnesium stearate, specifically, as recited in claim 1. As such, Saslawski and the PDR, alone or in combination with any of the other cited references, do not render obvious any of the instant claims.

In view of the foregoing, the cited references do not render obvious the claimed invention. Accordingly, Applicants request withdrawal of the obviousness rejection.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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